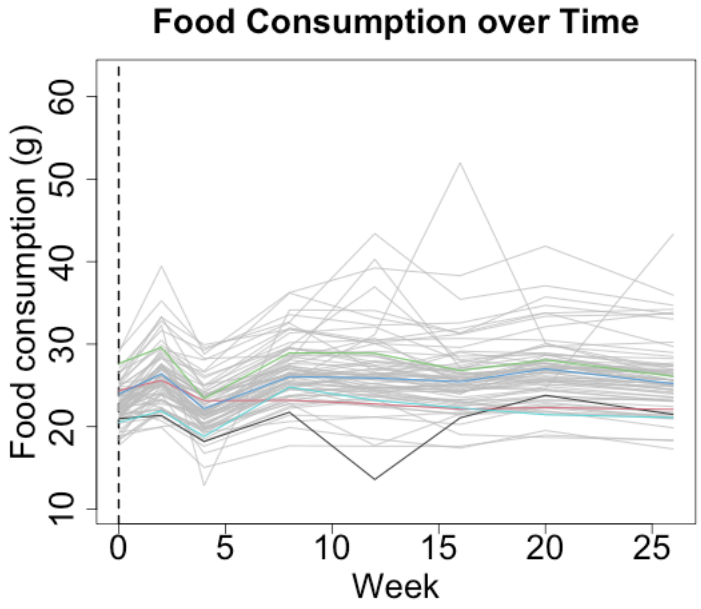
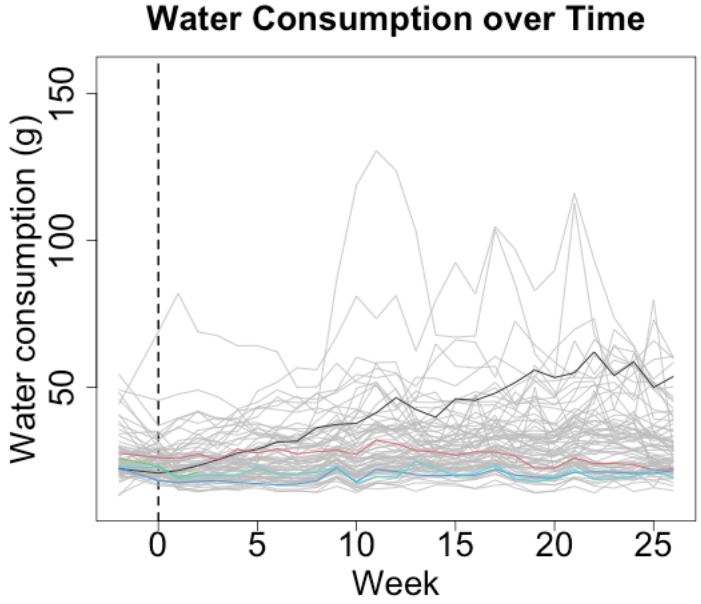
Appendix A

Fig S1

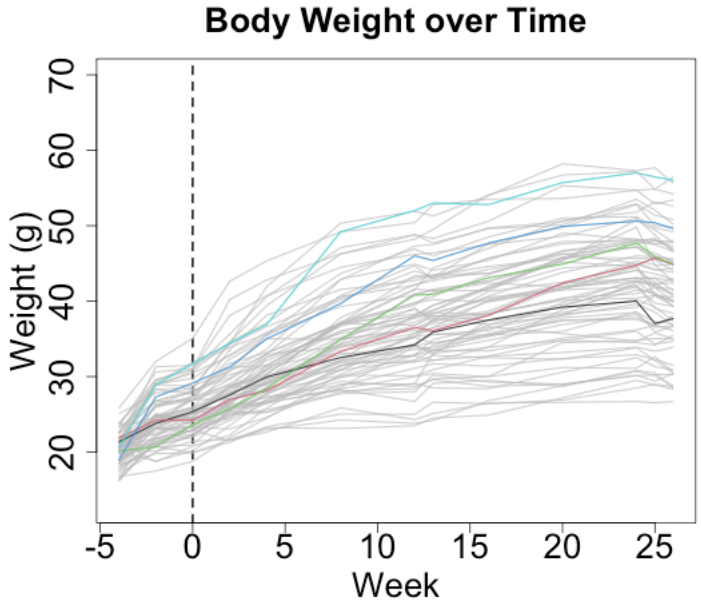
a) Individual time series of food consumption over time, with five random series highlighted in color



b) Individual time series of water consumption over time, with five random series highlighted in color



c) Individual time series of body weight over time, with five random series highlighted in color



d) Individual time series of body fat percentage over time, with five random series highlighted in color

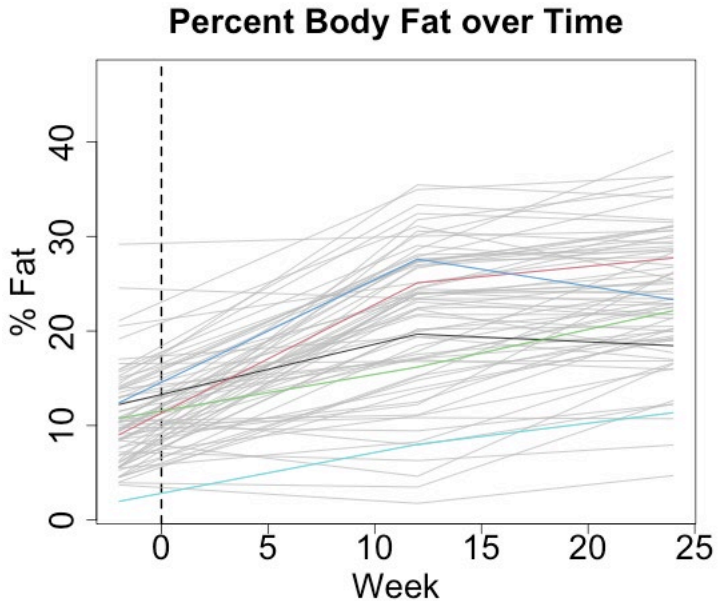
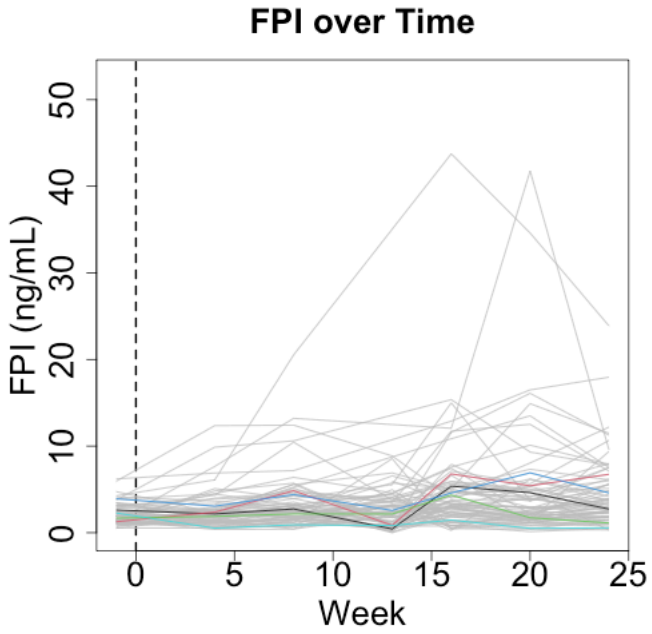
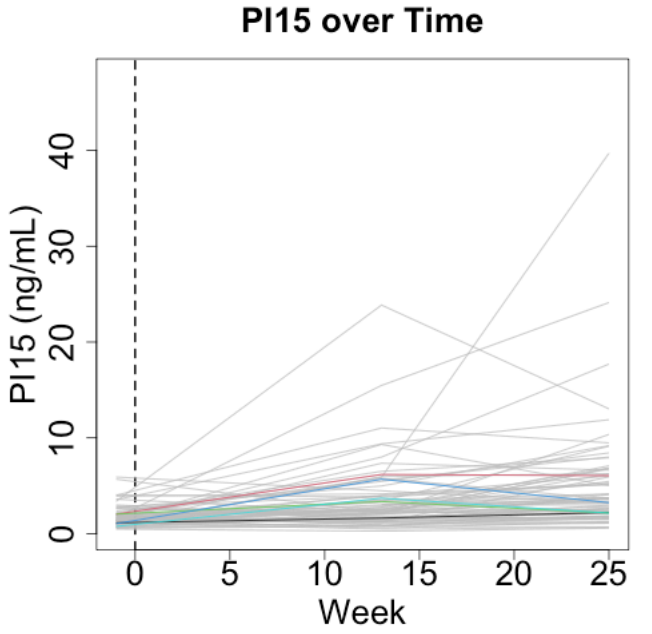


Fig S2

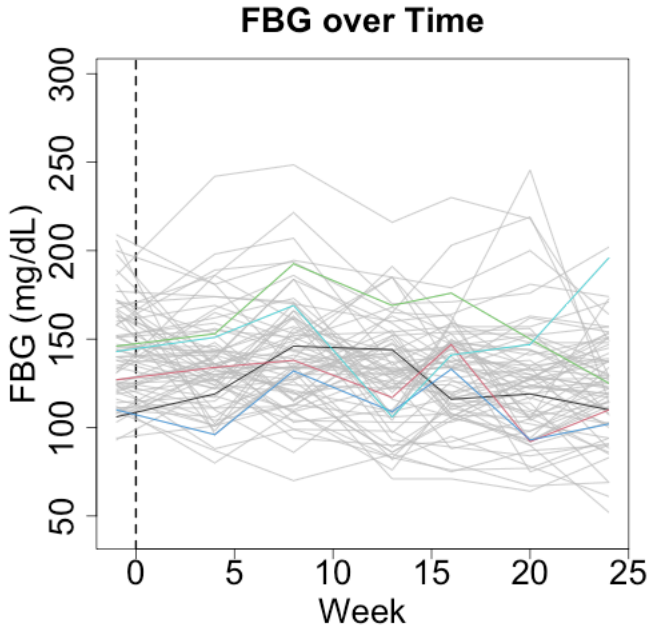
a) Individual time series of FPI over time, with five random series highlighted in color



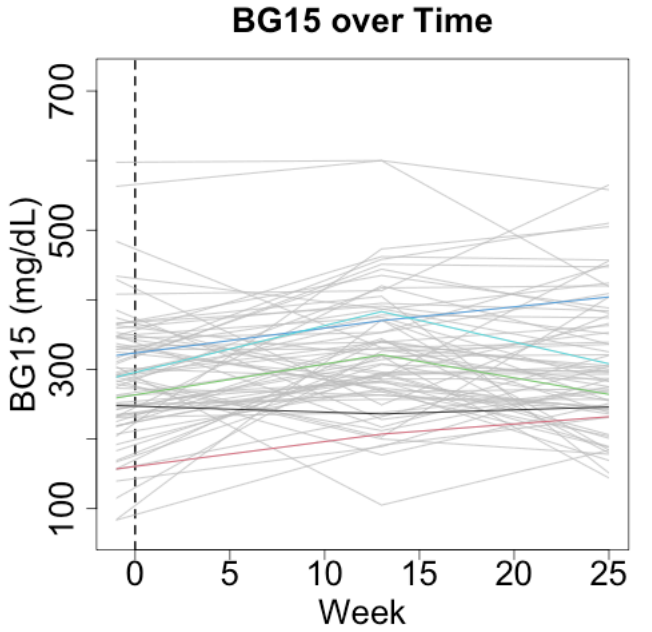
b) Individual time series of PI15 over time, with five random series highlighted in color



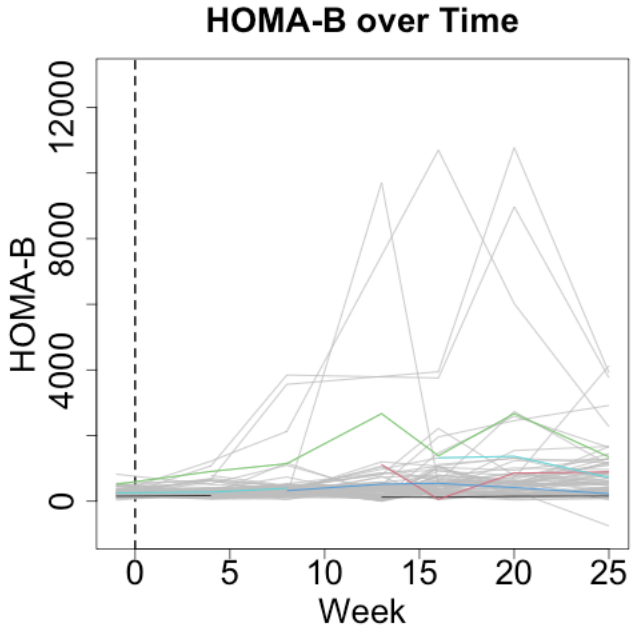
c) Individual time series of FBG over time, with five random series highlighted in color



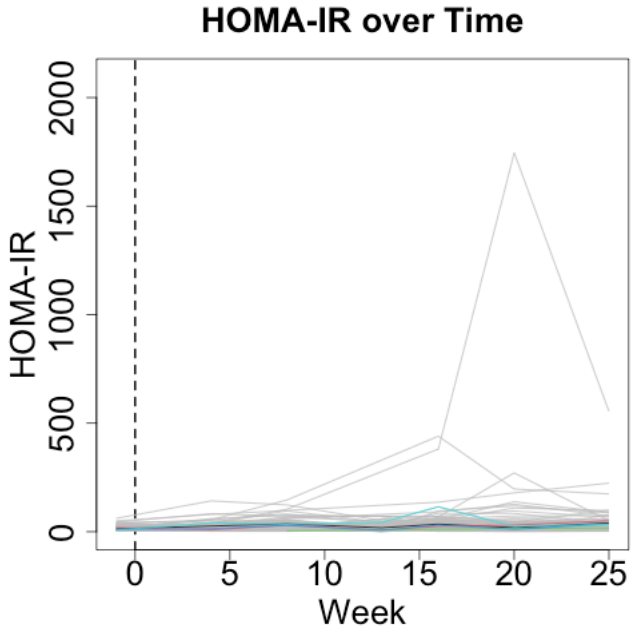
d) Individual time series of BG15 over time, with five random series highlighted in color



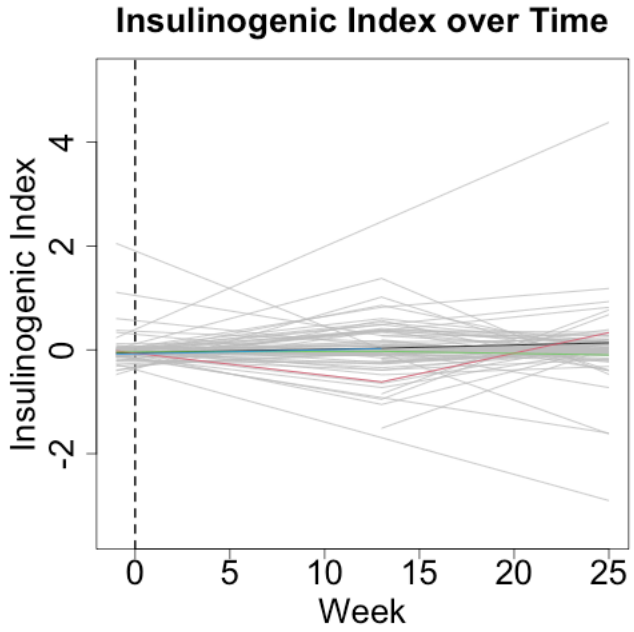
e) Individual time series of HOMA-B over time, with five random series highlighted in color



f) Individual time series of HOMA-IR over time, with five random series highlighted in color



g) Individual time series of insulinogenic index over time, with five random series highlighted in color



Fasting plasma insulin (FPI), week 25

Table S1: Association between iAs exposure and FPI, with sample GUDA_1001 removed

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	1.120	0.104	10.794	<0.001
$\log(FPI_{week\text{-}1})$	0.219	0.129	1.705	0.093
$Weight^{\dagger}_{week25}$	0.680	0.107	6.331	<0.001
$iAs^{\dagger}_{cumulative\_week25}$	-0.155	0.084	-1.832	0.072
$\%fat^{\dagger}_{week24}$	0.202	0.099	2.037	0.046
$iAs^{\dagger}_{cumulative\_week25} \times \%fat^{\dagger}_{week24}$	0.289	0.094	3.055	0.003

†centered and scaled

Table S2: Association between iAs exposure and FPI, with sample GUDA_1001 included

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	1.075	0.124	8.636	<0.001
$\log(FPI_{week\text{-}1})$	0.220	0.155	1.424	0.160
$Weight^{\dagger}_{week25}$	0.682	0.129	5.276	<0.001
$iAs^{\dagger}_{cumulative\_week25}$	-0.135	0.101	-1.329	0.189
$\%fat^{\dagger}_{week24}$	0.152	0.119	1.279	0.206

$iAs^{\dagger}_{cumulative\_week25} \times \%fat^{\dagger}_{week24}$	0.286	0.114	2.514	0.015

†centered and scaled

Table S3: Association between liver metabolites and FPI, with sample GUDA_1001 removed

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	1.205	0.615	1.959	0.054
$Weight^{\dagger}_{week25}$	0.562	0.098	5.735	<0.001
$\%fat^{\dagger}_{week24}$	-1.437	0.655	-2.196	0.032
$pDMAs_{liver}$	0.065	0.838	0.077	0.939
$pDMAs_{liver} \times \%fat^{\dagger}_{week24}$	2.217	0.915	2.424	0.018

†centered and scaled

Table S4: Association between liver metabolites and FPI, with sample GUDA_1001 included

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	1.219	0.723	1.687	0.096
$Weight^{\dagger}_{week25}$	0.579	0.115	5.030	<0.001
$\%fat^{\dagger}_{week24}$	-1.382	0.769	-1.796	0.077
$pDMAs_{liver}$	-0.009	0.985	-0.009	0.993
$pDMAs_{liver} \times \%fat^{\dagger}_{week24}$	2.063	1.075	1.919	0.059

†centered and scaled

15-minute plasma insulin (PI15), week 25

Table S5: Association between iAs exposure and PI15, with sample GUDA_1001 removed

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	1.063	0.082	12.967	<0.001
$\log(PI15_{week\text{-}1})$	0.403	0.122	3.298	0.002
$Weight^{\dagger}_{week25}$	0.551	0.105	5.228	0.000
$iAs^{\dagger}_{cumulative\_week25}$	-0.042	0.085	-0.501	0.618
$\%fat^{\dagger}_{week24}$	0.167	0.104	1.612	0.112
$iAs^{\dagger}_{cumulative\_week25} \times \%fat^{\dagger}_{week24}$	0.168	0.108	1.560	0.124

†centered and scaled

Table S6: Association between iAs exposure and PI15, with sample GUDA_1001 included

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	1.080	0.080	13.473	<0.001
$\log(PI15_{week\text{-}1})$	0.399	0.119	3.352	0.001
$Weight^{\dagger}_{week25}$	0.548	0.103	5.343	0.000
$iAs^{\dagger}_{cumulative\_week25}$	-0.050	0.083	-0.606	0.547
$\%fat^{\dagger}_{week24}$	0.191	0.101	1.885	0.064

$iAs^{\dagger}_{cumulative\_week25} \times$ $\%fat^{\dagger}_{week24}$	0.176	0.105	1.677	0.099

†centered and scaled

Fasting blood glucose (FBG), week 25

Table S7: Association between iAs exposure and FBG

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	83.223	17.452	4.769	<0.001
FBG_{week-1}	0.286	0.121	2.362	0.021
$iAs^{\dagger}_{cumulative\_week25}$	-3.505	3.422	-1.024	0.309

†centered and scaled

15 minute blood glucose (BG15), week 25

Table S8: Association between iAs exposure and BG15

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	214.628	33.947	6.322	<0.001
$BG15_{week-1}$	0.385	0.108	3.561	0.001
$Weight^{\dagger}_{week25}$	-3.724	15.993	-0.233	0.817
$\%fat^{\dagger}_{week24}$	-2.282	14.653	-0.156	0.877
$iAs^{\dagger}_{cumulative\_week25}$	-18.221	12.729	-1.431	0.157
$Weight^{\dagger}_{week25} \times \%fat^{\dagger}_{week24}$	-24.801	10.969	-2.261	0.027

†centered and scaled

Homeostatic model for beta cell function (HOMA-B), week 25

Table S9: Association between iAs exposure and HOMA-B, with sample GUDA_1060 removed

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	590.977	117.064	5.048	<0.001
$Weight^{\dagger}_{week25}$	465.851	126.220	3.691	<0.001
$iAs^{\dagger}_{cumulative\_week25}$	-91.721	152.083	-0.603	0.548
$iAs^{\dagger}_{cumulative\_week25} \times Weight^{\dagger}_{week25}$	362.776	114.009	3.182	0.002

†centered and scaled

Table S10: Association between iAs exposure and HOMA-B, with sample GUDA_1060 included

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	623.348	199.105	3.131	0.003
$Weight^{\dagger}_{week25}$	802.186	208.956	3.839	<0.001
$iAs^{\dagger}_{cumulative\_week25}$	-229.301	257.946	-0.889	0.377
$iAs^{\dagger}_{cumulative\_week25} \times Weight^{\dagger}_{week25}$	650.506	189.285	3.437	0.001

†centered and scaled

Homeostatic model for insulin resistance (HOMA-IR), week 25

Table S11: Association between iAs exposure and HOMA-IR, with sample GUDA_1060 removed

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	34.089	3.933	8.668	<0.001
$Weight^{\dagger}_{week25}$	21.034	4.241	4.960	<0.001
$iAs^{\dagger}_{cumulative\_week25}$	-5.944	5.109	-1.163	0.249
$iAs^{\dagger}_{cumulative\_week25} \times Weight^{\dagger}_{week25}$	6.726	3.830	1.756	0.084

†centered and scaled

Table S12: Association between iAs exposure and HOMA-IR, with sample GUDA_1060 included

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	35.404	7.641	4.634	<0.001
$Weight^{\dagger}_{week25}$	34.697	8.019	4.327	<0.001
$iAs^{\dagger}_{cumulative\_week25}$	-11.533	9.899	-1.165	0.248
$iAs^{\dagger}_{cumulative\_week25} \times Weight^{\dagger}_{week25}$	18.414	7.264	2.535	0.013

†centered and scaled

<u>Insulinogenic index, week 25</u>

Table S13: Association between iAs exposure and insulinogenic index, with sample GUDA_1060 removed

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	0.034	0.088	0.386	0.701
$iAs^{\dagger}_{cumulative\_week25}$	0.164	0.091	1.795	0.077

†centered and scaled

Table S14: Association between iAs exposure and insulinogenic index, with sample GUDA_1060 included

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	-0.326	0.378	-0.863	0.391
$iAs^{\dagger}_{cumulative\_week25}$	-0.365	0.391	-0.934	0.354

†centered and scaled

Table S15: Association between liver metabolites and HOMA-IR, with sample GUDA_1060 removed

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	-61.649	68.798	-0.896	0.373
$pDMAs_{liver}$	144.354	93.619	1.542	0.128

Table S16: Association between liver metabolites and HOMA-IR, with sample GUDA_1060 included

	Estimate	Std. Error	t value	Pr(>|t|)

Intercept	-31.705	35.224	-0.900	0.371
$pDMAs_{liver}$	93.693	47.979	1.953	0.055

Appendix B

The Non-obese Diabetic (NOD/ShiLtJ) and New Zealand Obese (NZO/HILtJ) strains are two of the eight parents of the multiparent Diversity Outbred (DO) population. These strains were bred to be models of type I diabetes and obesity (and thus type II diabetes), respectively. A potential concern is that imbalances in these founder contributions in the DO samples could confound the observed relationships, if these founder contributions are associated with the diabetes outcomes of interest. Of note, NOD and NZO are highly polygenic inbred models of diabetes and obesity, respectively. Presumably, they manifest their extreme outcomes due to the combined recessive and epistatic effects of a large number of loci. While we might expect strong effects of the founder contributions to obtain in an inbred multiparent population like the Collaborative Cross (CC), we did not anticipate this to be the case in the outbred DO.

To test this hypothesis, we first genotyped our DO samples on MiniMUGA, the most recent iteration of the Mouse Universal Genotyping Array (MUGA)[1]. Of the more than 11,000 probes on this array, 1050 were found to be diagnostic for the eight DO founder strains—that is, these probes constitute the diagnostic markers that can uniquely ascribe a locus to exactly one of these founders. We then thinned these markers to disallow adjacent markers that contained identical information and were within 30 kilobases of each other. Further, since it is inherited intact from the father, we retained a single marker on the Y chromosome for each founder. Similarly, since it is inherited intact from the mother, we retained a single mitochondrial marker for each of the four founders that the array is able to identify (NZO, CAST, PWK, and WSB). We note also that the array was able to

[1]Sigmon, John Sebastian, et al. "Content and performance of the minimuga genotyping array: a new tool to improve rigor and reproducibility in mouse research." *Genetics* 216.4 (2020): 905-930.

identify seven of the eight founders on chromosomes 11 and 17 (all but WSB and PWK, respectively). We define $x_{ijk} \in \{0,1,2\}$ as the number of alleles attributable to founder j at locus k for sample i. That is

i indexes sample, $i = 1, \ldots, 75$

j indexes founder strain, $j = 1, \ldots, 8$

k indexes a fully informative non-mitochondrial locus, $k = 1, \ldots n_j$ where n_j is the number of diagnostic markers for founder j

We then defined a score for strain j of sample i as d_{ij}, as follows:

$$d_{ij} = \sum_{c \notin \{11,17,M\}} \sum_{k=1}^{n_k^c} x_{ijk}^c + \frac{7}{8} \sum_{c \in \{11,17\}} \sum_{k=1}^{n_k^c} x_{ijk}^c + \frac{1}{2} x_{ij}^M$$

where the superscript c indexes chromosome. As shown, the alleles are weighted in direct proportion to the number of strains that can be identified on each chromosome. The distributions of the NOD and NZO scores were reasonably bell-shaped, as shown in Figures B1 and B2 below.

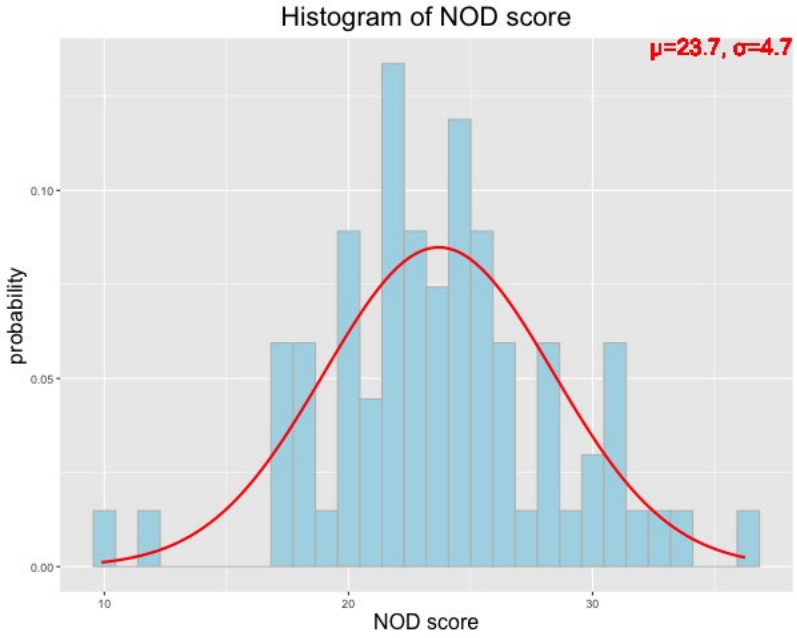


Figure B1: Histogram of NOD score with normal density overlayed (with the estimated mean and standard deviation recorded in the upper right corner)

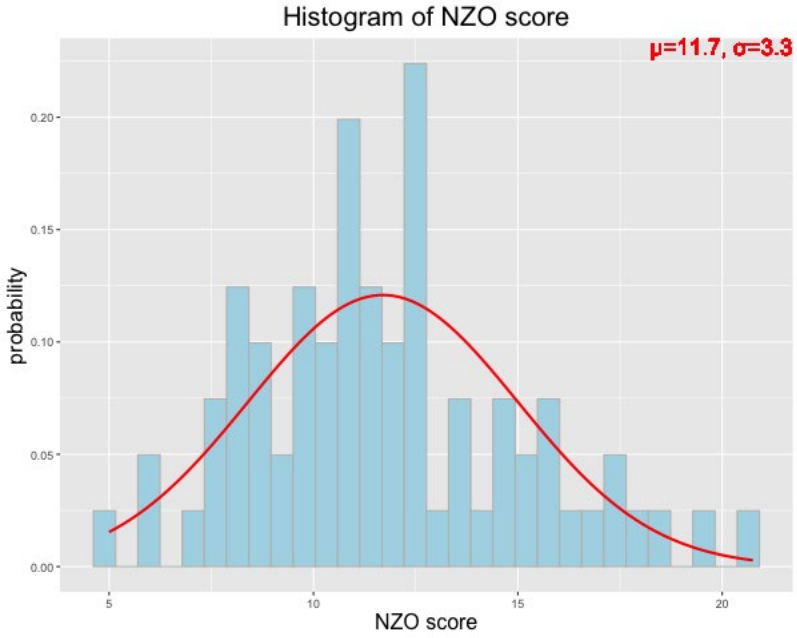


Figure B2: Histogram of NZO score with normal density overlayed (with the estimated mean and standard deviation recorded in the upper right corner)

An obvious means of testing our hypothesis is to investigate the relationship between our derived NZO score and body weight/adiposity in the DO samples. These relationships are visualized in figures B1 and B2 below. The lack of significant associations supports the notion that body weight and adiposity are highly polygenic traits, and that in the DO, the lack of combined recessive and epistatic effects obviates an association between NZO contribution and body weight/adiposity.

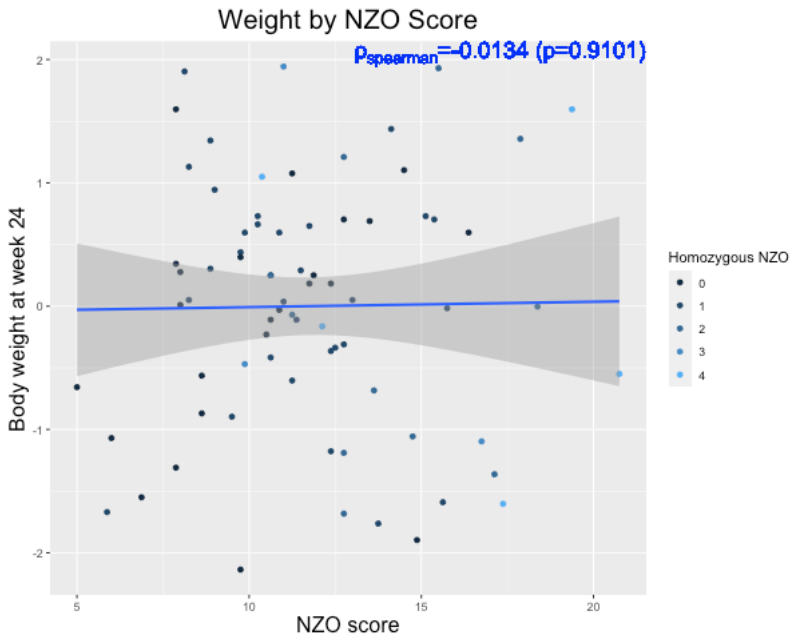


Figure B3: Scatter plot visualizing the association between the NZO score and body weight (standardized) at week 24. The slope of the line of best fit corresponds to the coefficient from a linear model regressing body weight on NZO score, and the Spearman correlation coefficient is recorded in the upper right. The shading represents the number of homozygous NZO alleles in each sample.

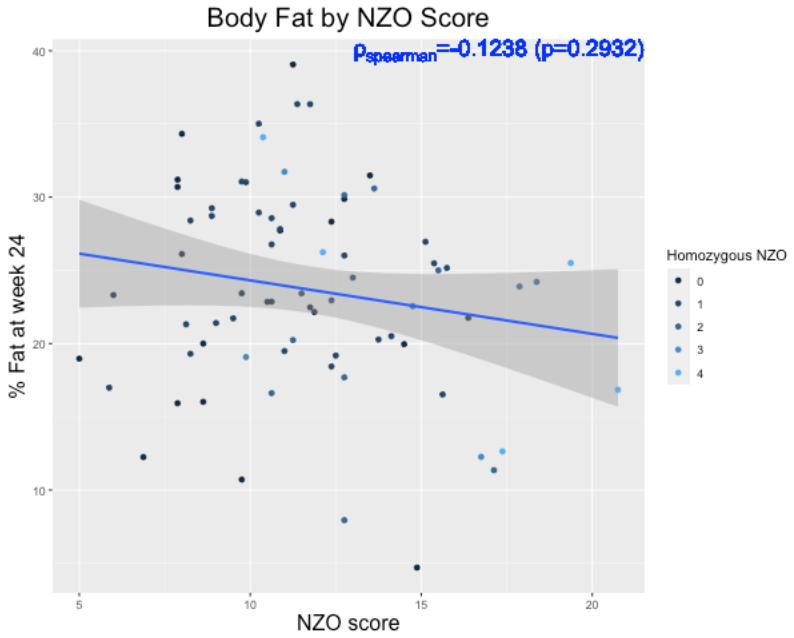


Figure B4: Scatter plot visualizing the association between the NZO score and adiposity (%body fat) at week 24. The slope of the line of best fit corresponds to the coefficient from a linear model regressing adiposity on NZO score, and the Spearman correlation coefficient is recorded in the upper right. The shading represents the number of homozygous NZO alleles in each sample.

We applied the same logic to investigate whether a higher combined contribution of NZO and NOD was associated with log(FPI) and log(PI15) at week 25. Before summing them, the NOD and NZO scores were normalized to put the founder contributions on the same scale. This sum was then normalized and plotted against log(FPI) and log(PI15) at week 25 in Figures B5 and B6. We similarly observed no significant relationships, militating against the concern that the founder contributions are confounders of our relationships of interest.

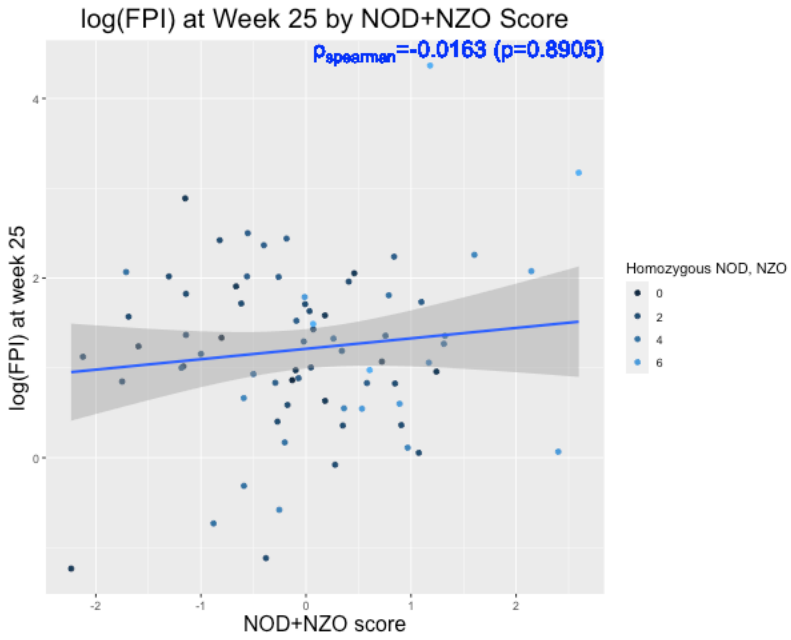


Figure B5: Scatter plot visualizing the association between the normalized NOD+NZO score and log(FPI) at week 25. The slope of the line of best fit corresponds to the coefficient from a linear model regressing log(FPI) on NOD+NZO score, and the Spearman correlation

coefficient is recorded at upper right. The shading represents the number of homozygous NOD or NZO alleles in each sample.

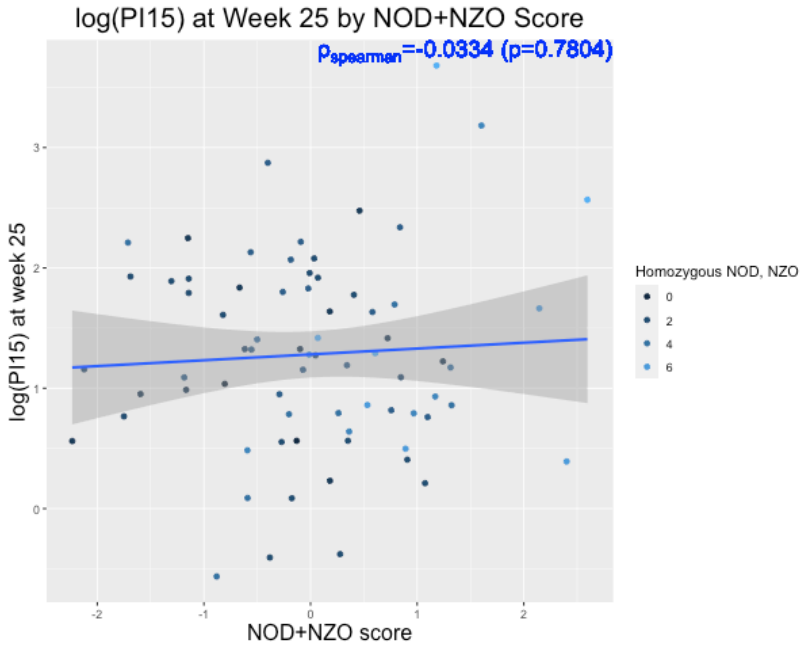


Figure B6: Scatter plot visualizing the association between the normalized NOD+NZO score and log(PI15) at week 25. The slope of the line of best fit corresponds to the coefficient from a linear model regressing log(PI15) on NOD+NZO score, and the Spearman correlation coefficient is recorded at upper right. The shading represents the number of homozygous NOD or NZO alleles in each sample.